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Prospective Study of Long-Term Impact of Adjuvant High-Dose and Conventional-Dose Chemotherapy on Health-Related Quality of Life

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ABSTRACT

Purpose

To evaluate and compare health-related quality of life (HRQOL) after conventional- and high-dose adjuvant chemotherapy in patients with high-risk breast cancer.

Patients and Methods

Patients were randomly assigned to either a conventional or high-dose chemotherapy regimen; both regimens were followed by radiotherapy and tamoxifen. HRQOL was evaluated until disease progression using the Short Form-36 (SF-36), Visual Analog Scale, and Rotterdam Symptom Checklist and assessed every 6 months for 5 years after random assignment. For the SF-36, data from healthy Dutch women with the same age distribution served as reference values.

Results

Eight hundred four patients (conventional-dose chemotherapy, $n = 405$; high-dose chemotherapy, $n = 399$) were included. Median follow-up time was 57 months. Directly after high-dose chemotherapy, HRQOL decreased more compared with conventional chemotherapy for all SF-36 subscales. After 1 year, the reference value of healthy women was reached in both groups. Small differences were observed between the two groups in the role-physical and role-emotional subscales, but 1 year after treatment, these differences were minor and not clinically relevant. During follow-up, patients with a lower educational level and many complaints before chemotherapy experienced a worse HRQOL.

Conclusion

Shortly after high-dose chemotherapy, HRQOL was more affected than after conventional-dose chemotherapy. One year after random assignment, differences were negligible. Identifying patients who have a higher chance of persistent impaired quality of life after treatment (which, in the present study, included patients with a lower educational level and many complaints before chemotherapy) is important and may open the way for better patient-tailored prevention strategies.

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INTRODUCTION

Adjuvant therapy is administered increasingly to women with breast cancer, resulting in delayed disease recurrence and improved survival. Because of the dismal prognosis of patients with extensive axillary nodal involvement, over the last 10 years, a variety of new treatment regimens has been tested. These include adjuvant dose-dense as well as high-dose chemotherapy with hematopoietic stem-cell reinfusion. A number of randomized studies have been performed.¹ A recent meta-analysis shows a significant benefit in event-free survival for the high-dose group at 3 and 4 years. Overall survival rates

were not significantly different, but most studies are still immature.¹

Relatively little is known about the long-term effects of adjuvant therapy on patients' well-being. Long-term data concerning health-related quality of life (HRQOL) in breast cancer patients after chemotherapy, particularly after high-dose chemotherapy, are limited.²⁻¹⁰ Most studies used cross-sectional designs with small and heterogeneous patient samples and relatively short follow-up.

In a Dutch randomized, multicenter study, high-dose chemotherapy improved relapse-free survival of stage II and III breast cancer patients with 10 or more positive axillary lymph nodes.¹¹ An

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update showed a trend for a better relapse-free survival in the high-dose arm. For the 621 patients with *HER2/neu*-negative disease there was a relapse-free survival and survival benefit with high-dose therapy.¹² HRQOL was included as a secondary end point. In this article, we report the longitudinal HRQOL results of this trial.

PATIENTS AND METHODS

Patients

Patients with stage II or III breast cancer were eligible for the trial if they had \geq four positive axillary lymph nodes, had an Eastern Cooperative Oncology Group-Zubrod performance status of 0 or 1, and were younger than 56 years. Before random assignment, patients were stratified according to age (< 50 v ≥ 50 years), menopausal status (premenopausal v postmenopausal), number of lymph node metastases (four to nine v ≥ 10 metastases), and tumor size (pT1 v pT2 v pT3).^{11,12}

Treatment Regimens

Patients received either five cycles of fluorouracil (500 mg/m²), epirubicin (90 mg/m²), and cyclophosphamide (500 mg/m²) or four cycles of the same chemotherapy followed by one cycle of high-dose chemotherapy consisting of cyclophosphamide (6 g/m²), thiotepa 480 (mg/m²), and carboplatin (1,600 mg/m²) over 4 days and autologous peripheral stem-cell reinfusion. The original protocol included tamoxifen 40 mg daily for 2 years. During the trial, it became clear that 5 years of tamoxifen were superior to 2 years. Therefore, patients with hormone receptor-positive cancer continued to receive tamoxifen for a total of 5 years.¹¹ The medical ethical committee of the participating hospitals approved the study, and all patients gave informed consent.

HRQOL

HRQOL was assessed by means of a Visual Analog Scale (VAS) for general health perception, the Short Form-36 Health Survey (SF-36), and the Rotterdam Symptom Checklist (RSCL). The VAS scale ranged from 0 (worst imaginable health state) to 100 (best imaginable health state).

The SF-36 is organized into eight scales assessing physical functioning, role-physical, bodily pain, general health, mental health, role-emotional, social functioning, and vitality.¹³ Scale scores range from 0 to 100, with higher scores representing a higher level of functioning. Reference data for healthy Dutch women (mean age, 47 years; range, 16 to 96 years) were available for comparison.¹⁴ The outcome of the SF-36 is age dependent. The age distribution in this study is skewed (range, 24 to 56 years). Therefore, six age categories were identified. Within each age category, one reference healthy woman could be sampled for every four breast cancer patients. This way, 199 reference women were identified, and their data on the eight scales of the SF-36 were used. The calculated mean values were used as reference values.

The RSCL is a cancer-specific tool to measure psychological and physical distress in cancer patients. Patients indicated the degree to which they have been bothered by the 30 indicated symptoms in the past week.¹⁵ The distribution of the RSCL item scores was highly skewed. Therefore, the 4-point Likert-type response scales were collapsed into the presence/absence of each symptom. Sociodemographic characteristics including age, education, marital status, number of children living at home, and employment status were collected at baseline.

Follow-Up

Patients received the questionnaires by mail before random assignment, after chemotherapy completion, after radiotherapy completion, and every 6 months thereafter. The data reported cover a maximum of 5 years after random assignment (maximum of 12 assessments).

Statistical Analysis

The planned sample size was based on the primary end points of disease-free and overall survival. The HRQOL data were analyzed according to the intent-to-treat principle. Data of patients who had not yet reached the 5-year follow-up were included in the analysis until their last follow-up. Questionnaires of patients who experienced relapse or died within 5 years after random assignment were included in the analyses until disease relapse or death. Statistical analysis was performed using SPSS version 11.0 (SPSS Inc, Chicago, IL) and Multi Level-wiN version 1.10 (Bristol Institute of Public Affairs, Bristol, United Kingdom).¹⁶

Student's *t* test for independent samples and the χ^2 test were used to compare sociodemographic and baseline HRQOL scores of the two arms. At the 1-year follow-up, the *t* test was used to compare mean SF-36 scores of the two arms with those of the age-matched reference group from the general Dutch population.

Mixed-effects analysis of variance models for repeated measures was used to assess longitudinal HRQOL changes within and between treatment arms.¹⁷ At random assignment, there was no difference in HRQOL between the two groups. This information was put into the mixed-effects analysis. Age (> 50 v ≤ 50 years) and menopausal status were separately included as covariates. $P < .05$ was considered statistically significant.

Effect size is defined as the mean HRQOL score difference between the high-dose and conventional-dose groups divided by the standard deviation of the HRQOL scores of the total group at that measurement moment. A value of 0.2 to 0.5 is considered indicative of a small effect, 0.5 indicates a medium effect, and 0.8 indicates a large effect size.¹⁸

RESULTS

Patients

From August 1993 to July 1999, 885 patients were enrolled onto the clinical trial.^{11,12} The HRQOL component of the trial began after 47 patients had been entered. Of the remaining 838 patients, 34 (4%) did not participate (27 patients declined, and seven did not participate as a result of logistical reasons). Of the 804 patients who participated in the HRQOL study, 405 received conventional-dose chemotherapy, and 399 received high-dose chemotherapy. Forty-one patients randomly assigned to high-dose therapy did not receive this treatment.¹¹ According to the intent-to-treat principle, they were included in the high-dose arm for analysis. None of the patients randomly assigned to conventional-dose chemotherapy received high-dose chemotherapy.

Compliance With HRQOL Questionnaires

HRQOL data collected up to 5 years after random assignment were included in the analysis. The median follow-up time was 57 months. Figure 1 shows response rates for the HRQOL questionnaires at baseline and during follow-up. The overall response rate was 86% (range, 73% to 95%) at the various assessment points. No significant differences in compliance were observed between the treatment arms. Two hundred four patients (25%; 100 in conventional-dose group and 104 in high-dose group) had not yet reached the 5-year follow-up. At the time of analysis, 325 patients (40%; 156 in conventional-dose group and 169 in high-dose group) were disease free at 5 years of follow-up.

Sociodemographic Characteristics

Patient characteristics at random assignment were well balanced between the treatment arms (Table 1). At random assignment, 50% of the patients ($n = 400$) were employed, and 80% ($n = 646$) had children. There were no significant differences between the arms in the percentage of patients employed at random assignment or at 1 or 3 years after random assignment or in the number of hours per week worked. At follow-up, 34% of all patients reported working less (≤ 4 hours per week) than at trial entry, 48% indicated that this had not changed, and 18% worked more.

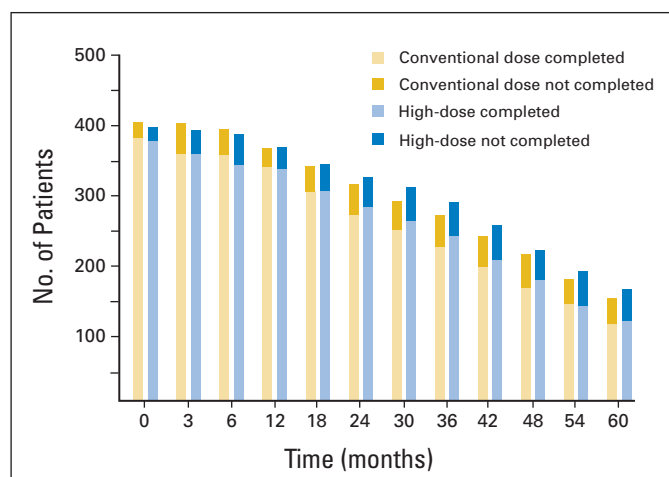


Fig 1. Number of patients in the conventional-dose and high-dose treatment groups who returned the health-related quality of life questionnaire during treatment and follow-up.

HRQOL Outcomes

VAS. The results of the mixed-effects model analysis for VAS scores and effect sizes over time for both arms are illustrated in Figure 2. At baseline, there was no statistically significant difference in VAS scores between the treatment arms. Until 24 months, the conventional-dose group scored statistically significantly higher than the high-dose group. Just after chemotherapy, there was a large effect size (0.82), and until 24 months, a small effect size (0.18 to 0.36) was seen. Thereafter, no significant between-group differences in VAS score were observed over time.

SF-36. The results of the mixed-effects models for all subscales of the SF-36 during follow-up in both arms are presented in

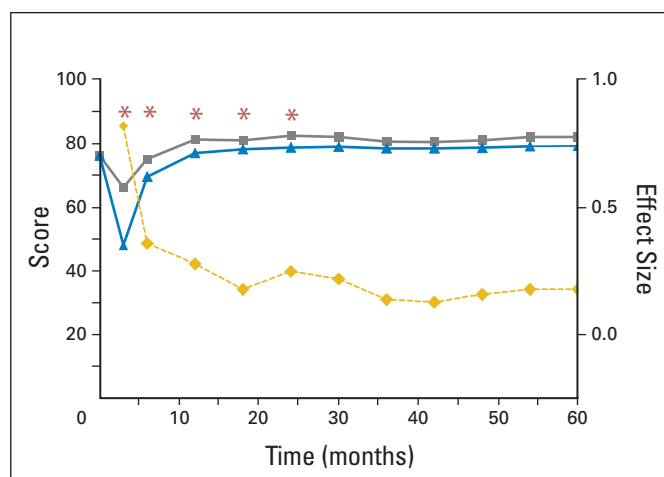


Fig 2. Mean scores of the Visual Analog Scale (VAS) in the high-dose group (▲) and conventional-dose group (■) at random assignment and during 5 years of follow-up and effect size (◆). The x axis shows time in months. Left y axis represents VAS score, and right y axis represents the effect size. Significant difference between the high-dose and conventional-dose groups is indicated with an asterisk (*).

Figure 3, as well as the normal reference values and the effect sizes. At baseline, there were no significant differences between the arms in SF-36 scores. Both patient groups scored lower on two SF-36 subscales, role-physical and role-emotional, than the general population reference sample.

Directly after chemotherapy, the high-dose group scored statistically significantly lower for all subscales, with effect sizes all greater than 0.5. Only the scores on general health did not differ between the two arms. For the subscales of mental health, role-emotional, social functioning, and bodily pain, no significant differences between the two arms were seen 6 months after random assignment and later, and effect sizes were always less than 0.20. At 2.5 years after random assignment, the high-dose group had lower scores for role-physical compared with the conventional-dose group, but the effect sizes during this period were less than 0.2.

For the subscales of physical functioning and vitality, a small but significant difference was observed between the two arms during the 5 years of follow-up. The effect sizes during those years were just greater than 0.20 for physical functioning and just less than 0.20 for vitality.

For all subscales, except for role-physical in both arms and physical functioning for the high-dose group, scores returned to normal or greater than reference values at 1 year. Thereafter, all HRQOL scores remained stable over the next 4 years.

Correlation between age, menopausal status in the SF-36, and VAS scores. The covariates of age and menopausal status had significant effects on the subscales of physical functioning and role-physical. In both arms, physical functioning scores of younger women (< 50 years at random assignment) were significantly higher compared with older women at all time points. From 1 to 5 years after random assignment, differences between younger and older women were statistically significant, but effect sizes were small. Patients who were postmenopausal at random assignment scored significantly lower on the role-physical subscale compared with patients who were premenopausal over the whole 5-year period.

RSCL. Tiredness, decreased sexual interest, sweating, and painful muscles were the most prevalent symptoms. The percentage of

Characteristic	No. of Patients	
	Conventional-Dose Group	High-Dose Group
Age, years		
Mean	44.5	44.7
Range	26-56	24-56
Have a partner		
Yes	356	359
No	34	25
Unknown	15	15
Have children		
Yes	330	316
No	61	69
Unknown	14	14
Menopausal status		
Premenopausal	334	343
Postmenopausal	56	49
Uncertain	15	24
Education		
None		1
Grammar school	16	17
High school	281	273
Entered some college	76	60
Completed college	17	34
Unknown	15	14

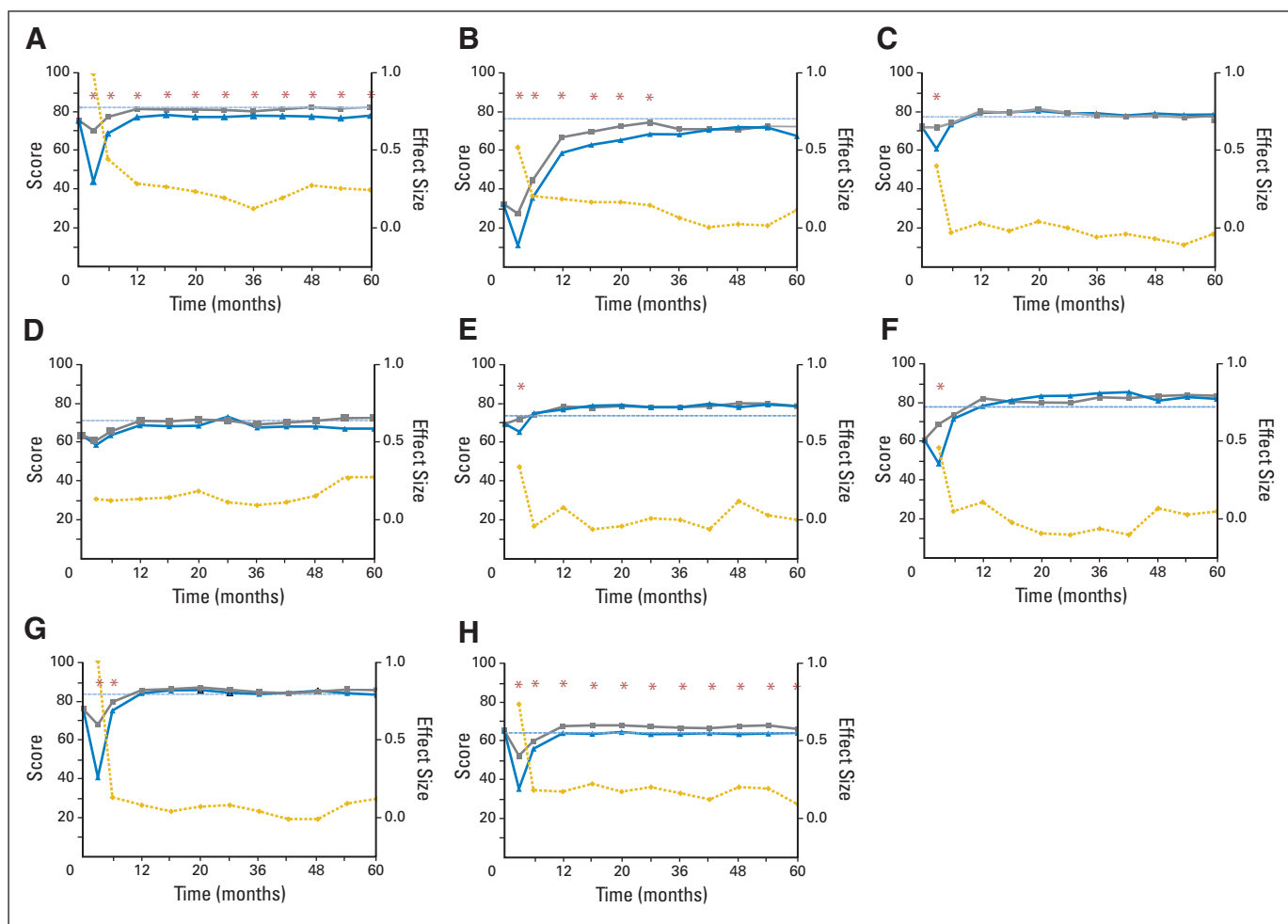


Fig 3. Mean Short Form-36 Health Survey (SF-36) subscales scores in the high-dose group (▲) and conventional-dose group (■) and reference values from age-corrected controls (---) and effect size (◆) at random assignment and during 5 years of follow-up. The x axis shows time in months. Left y axis represents SF-36 score, and right y axis represents effect size. Significant difference between the high-dose and conventional-dose groups is indicated with an asterisk (*).

patients reporting tiredness and decreased sexual interest over time is shown in Figure 4. Just after chemotherapy, the percentage of patients with physical symptoms was higher compared with baseline in both arms. Overall, the percentage of patients with symptoms was higher in the high-dose group. This difference was already largely reduced 6 months after random assignment. During the follow-up period, 10% of the patients ($n = 78$) experienced three or four of the most prevalent symptoms for more than half of the time. Compared with patients without this high frequency of complaints, these patients could only be distinguished by a lower education level. The seven items indicating psychological distress (irritability, worrying, depressed mood, nervousness, despairing about the future, tension, and anxiety) diminished in both arms from random assignment up to 1 year later and remained constant over the next 4 years. After 5 years, 244 patients completed HRQOL questionnaires, and 33% of the patients reported no symptoms, 17% experienced one symptom, 13% experienced two symptoms, 9% experienced three symptoms, and 28% experienced four or more symptoms of the RSCL.

Decreased sexual interest was the most prevalent symptom (36%). Patients with many symptoms (\geq four) and few symptoms (\leq three) showed no differences with regard to treatment arm, age,

employment status, number of working hours at random assignment, having children and children living at home, marital status, menopausal status at random assignment, or education level. Patients with many symptoms after 5 years scored significantly lower on all SF-36 subscales at random assignment and at the 11 measurement points thereafter compared with other patients. The only exception was role-physical at random assignment. In Figure 5, the scores over time for the subscale of bodily pain for the patients with many and few complaints are shown. The results for other subscales of SF-36 and VAS are comparable and not shown. Eighty percent of patients having \leq three symptoms of the RSCL at random assignment reported \leq three complaints after 5 years, and half of all patients scoring \geq four symptoms at random assignment scored \geq four symptoms after 5 years.

DISCUSSION

This prospective, longitudinal study describes HRQOL for 5 years after random assignment between conventional- and high-dose chemotherapy in a large group of disease-free, high-risk breast cancer patients. At random assignment, the HRQOL of patients was only

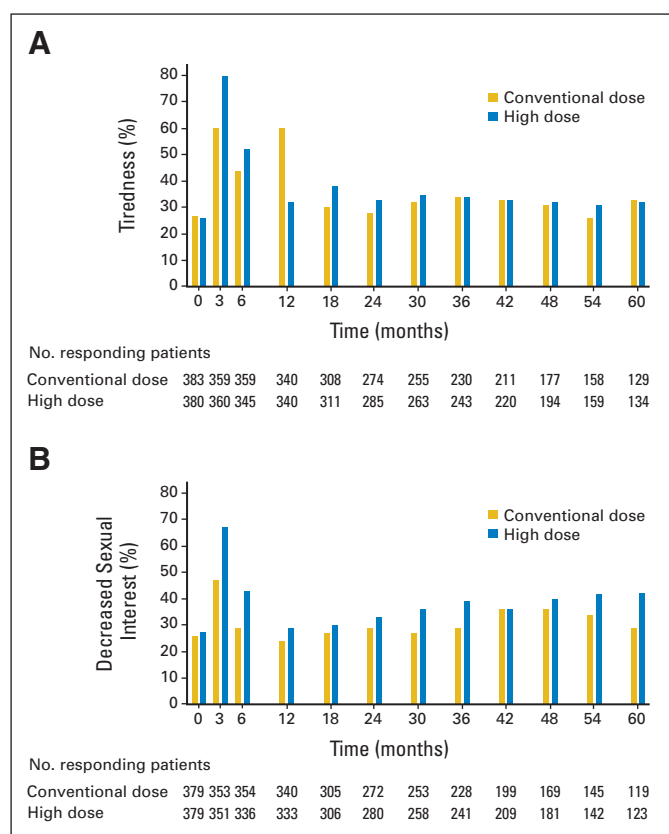


Fig 4. Percentage of patients reporting symptoms by the Rotterdam Symptom Checklist (3 = quite a bit, 4 = very much) at each assessment point for patients treated with conventional- or high-dose chemotherapy.

slightly different from an age- and sex-matched control group obtained from the general Dutch population. During the immediate post-treatment period, HRQOL was worse in the high-dose than in the conventional-dose treatment group. However, 1 year after random assignment, HRQOL in both groups was again comparable to

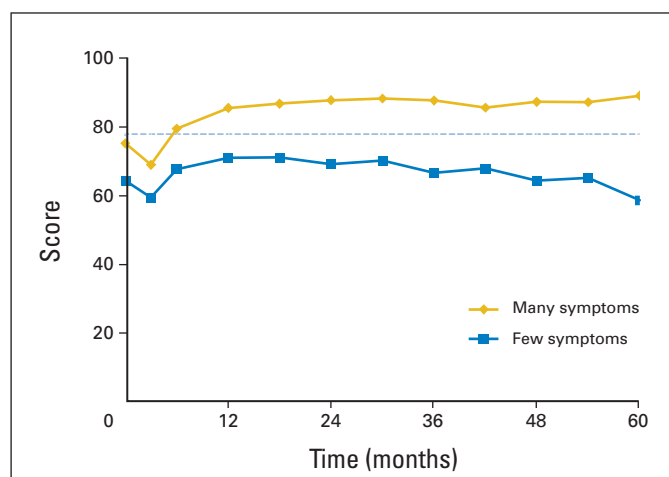


Fig 5. Mean scores of the Short Form-36 Health Survey subscale of bodily pain for patients with many (\geq four symptoms [\blacklozenge]) and few symptoms (\leq three symptoms; \blacksquare) and reference values from age-corrected controls (— — —) at random assignment and during 5 years of follow-up. The x axis shows time in months. The y axis represents bodily pain score.

the general population reference values, and these levels remained relatively constant over the next 4 years.

Comparison of HRQOL studies is relevant but can be hampered by differences in study designs and measures used.¹⁹ In the future, disease-specific questionnaires, such as the Functional Assessment of Cancer Therapy–Breast, might be able to detect additional differences that the SF-36, for example, does not reveal.

A small cross-sectional study in 43 patients with 2 years of median follow-up after high-dose chemotherapy reported higher HRQOL scores compared with patients receiving conventional-dose chemotherapy using the Functional Living Index Cancer questionnaire. However, the scores on this questionnaire differed only marginally between the two groups.²⁰ Another study, which compared pre- and post-treatment HRQOL, observed that disease-free breast cancer patients ($n = 24$) after high-dose chemotherapy had higher HRQOL than before treatment.³ The investigators excluded all patients who experienced relapse or died during follow-up from the analysis. To achieve an objective rating of HRQOL, data of all patients were included in our study until disease relapse or death.

Although research on HRQOL in breast cancer patients has become increasingly sophisticated, few longitudinal studies have assessed patients before and after treatment.^{7,9,10,21} Longitudinal HRQOL studies lay a considerable claim to the compliance of patients, requiring frequent HRQOL questionnaires to be returned.⁶ Objectively and compared with others, our overall response rate was high (86%).^{7,9,10} Most longitudinal HRQOL studies are analyzed with repeated-measurement analysis of variance, and one missing questionnaire will result in omitting all data of that particular patient. Analysis by mixed-effects models, as performed in our study, has the advantages that all data can be used and selection bias is excluded.

One large, randomized, prospective study with serial assessment points compared HRQOL of patients receiving adjuvant high-dose chemotherapy ($n = 197$) or tailored chemotherapy ($n = 211$). This study showed a larger decrease in HRQOL and faster recovery in the high-dose group compared with the tailored group during the first year.⁷ Similar to our findings, HRQOL had returned to baseline in both groups 1 year after treatment. The faster HRQOL recovery in the high-dose group can be explained by the fact that the tailored arm actually had received more chemotherapy over a longer period of time.⁷ Another prospective study compared HRQOL of breast cancer patients until 3 years after high-dose chemotherapy ($n = 106$) or intermediate-dose chemotherapy ($n = 104$). HRQOL was compromised transiently among patients in the high-dose group but not among patients in the intermediate-dose group.¹⁰ One explanation for this finding could be the fact that the first assessment took place 3 months after chemotherapy, thereby missing the transient decrease in HRQOL in the intermediate-dose group. Availability of HRQOL data of healthy women allowed us to interpret HRQOL in a more balanced manner. The HRQOL of our patients seemed to be comparable to that of healthy women of the same age. With frequent assessments, others found a decrease in HRQOL in both arms, similar to our observations.⁷ In another prospective longitudinal breast cancer study in 52 patients after high-dose chemotherapy, HRQOL was measured repeatedly from baseline over 2 years. HRQOL decreased but had returned to baseline 8 weeks after treatment.⁹ Although our study and the previously mentioned studies differ in many aspects, 1 year after treatment, no differences in HRQOL between the treatment groups or from baseline were found by all four studies.^{7,9,10}

In our study, patients generally reported a few (late) symptoms, but some complaints persisted for several years. Remarkably, single symptoms apparently did not have a severe influence on HRQOL. Decreased sexual interest was the most prevalent symptom. Impaired sexual functioning represents a well-known specific long-term sequela of breast cancer patients.^{4,9,22,23} In part, this can be a result of premature ovarian failure caused by chemotherapy.⁹ Tiredness, painful muscles, and sweating were also frequently reported. Interpreting these results is difficult because healthy postmenopausal women also commonly mention these symptoms. We have earlier shown that (lower) mental health was the strongest predictor for tiredness in a subpopulation of the current study.²⁴ Patients with repeated multiple complaints were, in the current analysis, characterized by a lower educational level. A few other studies have also observed this relationship. Kornblith et al²⁵ noticed that breast cancer survivors with a lower education level had more problems adapting to post-traumatic stress 20 years after adjuvant therapy. In a study of 2,208 women with breast cancer or at risk for breast cancer, women with a lower educational level were more likely to be bothered by symptoms.²⁶ In our study, the 10% of patients with repeated multiple complaints are characterized by a lower education level. In addition, for 5-year disease-free survivors, we analyzed whether complaints mentioned in the RSCL at random assignment predicted their HRQOL at 5 years. This analysis revealed that half of patients with four or more symptoms at 5 years also had many complaints at random assignment. This indicates that having complaints before chemotherapy predicts a worse HRQOL outcome.

The HRQOL of breast cancer patients in our study, 1 to 5 years after treatment, is comparable to healthy women. Only small, clinically irrelevant differences were observed between the treatment groups. Therefore, the impact of both chemotherapy regimens on HRQOL is clearly less severe than expected. HRQOL recovers swiftly after adjuvant treatment. Women with poor prognosis breast cancer,

who are engaged in intensive treatment protocols, tend to adapt to their new situation and to modify their reference points. The emotional and social support of relatives, friends, and medical staff can contribute to their adaptation.²⁷ Identifying patients who have a higher chance of persistent impaired quality of life after treatment may open the way for better patient-tailored prevention strategies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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REFERENCES

- Farquhar CM, Marjoribanks J, Lethaby A, et al: High dose chemotherapy for poor prognosis breast cancer: Systematic review and meta-analysis. *Cancer Treat Rev* 33:325-337, 2007
- Carlson LE, Koski T, Gluck S: Longitudinal effects of high-dose chemotherapy and autologous stem cell transplantation on quality of life in the treatment of metastatic breast cancer. *Bone Marrow Transplant* 27:989-998, 2001
- McQuellon RP, Craven B, Russell GB, et al: Quality of life in breast cancer patients before and after autologous bone marrow transplantation. *Bone Marrow Transplant* 18:579-584, 1996
- Winer EP, Lindley C, Hardee M, et al: Quality of life in patients surviving at least 12 months following high dose chemotherapy with autologous bone marrow support. *Psychooncology* 8:167-176, 1999
- Hann DM, Jacobsen PB, Martin SC, et al: Quality of life following bone marrow transplantation for breast cancer: A comparative study. *Bone Marrow Transplant* 19:257-264, 1997
- Bottomley A, Therasse P: Quality of life in patients undergoing systemic therapy for advanced breast cancer. *Lancet Oncol* 3:620-628, 2002
- Brandberg Y, Michelson H, Nilsson B, et al: Quality of life in women with breast cancer during the first year after random assignment to adjuvant treatment with marrow-supported high-dose chemotherapy with cyclophosphamide, thiotepa, and carboplatin or tailored therapy with fluorouracil, epirubicin, and cyclophosphamide: Scandinavian Breast Group Study 9401. *J Clin Oncol* 21:3659-3664, 2003
- Ganz PA, Desmond KA, Leedham B, et al: Quality of life in long-term, disease-free survivors of breast cancer: A follow-up study. *J Natl Cancer Inst* 94:39-49, 2002
- Conner-Spady BL, Cumming C, Nabholz JM, et al: A longitudinal prospective study of health-related quality of life in breast cancer patients following high-dose chemotherapy with autologous blood stem cell transplantation. *Bone Marrow Transplant* 36:251-259, 2005
- Peppercorn J, Herndon J, Kornblith AB, et al: Quality of life among patients with stage II and III breast carcinoma randomized to receive high-dose chemotherapy with autologous bone marrow support or intermediate-dose chemotherapy. *Cancer* 104:1580-1589, 2005
- Rodenhuis S, Bontenbal M, Beex LV, et al: High-dose chemotherapy with hematopoietic stem-cell rescue for high-risk breast cancer. *N Engl J Med* 349:7-16, 2003
- Rodenhuis S, Bontenbal M, van Hoesel QG, et al: Efficacy of high-dose alkylating chemotherapy in HER2/neu-negative breast cancer. *Ann Oncol* 17:588-596, 2006
- Ware JE, Snow KK, Kosinski M, et al: SF-36 Health Survey, Manual and Interpretation Guide. Boston, MA, The Health Institute, New England Medical Center, 1993
- Aaronson NK, Muller M, Cohen PD, et al: Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 51:1055-1068, 1998
- Fallowfield LJ: Assessment of quality of life in breast cancer. *Acta Oncol* 34:689-694, 1995
- Rasbash J, Steele P, Browne W, et al: A User's Guide to MLwiN. London, United Kingdom, Institute of Education, 2000
- Gueorguieva R, Krystal JH: Move over ANOVA: Progress in analyzing repeated-measures data and its reflection in papers published in the *Archives of General Psychiatry*. *Arch Gen Psychiatry* 61:310-317, 2004
- Cohen J: A power primer. *Psychol Bull* 112:155-159, 1992
- Partridge AH, Winer EP: Quality of life issues among women undergoing high-dose chemotherapy for breast cancer. *Breast Dis* 14:41-50, 2001

20. Peters WP, Ross M, Vredenburg JJ, et al: High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. *J Clin Oncol* 11:1132-1143, 1993
21. Bower JE: Prevalence and causes of fatigue after cancer treatment: The next generation of research. *J Clin Oncol* 23:8280-8281, 2005
22. Dorval M, Maunsell E, Deschenes L, et al: Long-term quality of life after breast cancer: Comparison of 8-year survivors with population controls. *J Clin Oncol* 16:487-494, 1998
23. Stead ML: Sexual dysfunction after treatment for gynaecologic and breast malignancies. *Curr Opin Obstet Gynecol* 15:57-61, 2003
24. Nieboer P, Buijs C, Rodenhuis S, et al: Fatigue and relating factors in high-risk breast cancer patients with adjuvant standard- or high-dose chemotherapy: A longitudinal study. *J Clin Oncol* 23:8296-8304, 2005
25. Kornblith AB, Herndon JE, Weiss RB, et al: Long-term adjustment of survivors of early-stage breast carcinoma, 20 years after adjuvant chemotherapy. *Cancer* 98:679-689, 2003
26. Stanton AL, Bernaards CA, Ganz PA: The BCPT symptom scales: A measure of physical symptoms for women diagnosed with or at risk for breast cancer. *J Natl Cancer Inst* 97:448-456, 2005
27. Macquart-Moulin G, Viens P, Palangie T, et al: High-dose sequential chemotherapy with recombinant granulocyte colony-stimulating factor and repeated stem-cell support for inflammatory breast cancer patients: Does impact on quality of life jeopardize feasibility and acceptability of treatment? *J Clin Oncol* 18:754-764, 2000

